Draft SPL Release 2 Implementation Guide for Highlights

1. Introduction

This document provides technical details on using SPL Release 2 for the changes in the FDA Requirements on the Content and Format of Labeling for Human Prescription Drug and Biological Products. The details for these changes are in the final rule published in the Federal Register, Volume 71, Number 15, Pages 3922-3997 (January 24, 2006). Among other things, the rule revises labeling regulations to require inclusion of Highlights and a table of contents for the Full Prescribing Information (FPI). In addition, certain labeling sections in the FPI are reorganized.

The scope in this document is limited to submission of SPL to FDA. Additional data elements included in SPL release 2 that are not covered in this document are not part of SPL submitted to FDA at this time and are outside the scope of this document. Instructions related to the information to include in Highlights are also outside the scope of this document. Details on controlled vocabulary referred to in this document are on the FDA Data Standards Council web site at http://www.fda.gov/oc/datacouncil. References for information on the content of labeling and examples of SPL XML are also posted on this web page.

2. Stylesheet and Schema

Information: The references to the SPL release 2 schema and FDA stylesheet.

Terminology: There is no controlled terminology for this information.

SPL location: This information is in the beginning of the SPL file.

XML details: Reference to the stylesheet and schema is provided as follows:

<?xml version="1.0" encoding="utf-8"?>

```
<?xml-stylesheet href="http://www.fda.gov/oc/datacouncil/stylesheets/spl/spl.xsl" type="text/xsl"?>
<document xmlns:voc="http://www.hl7.org/v3/voc" xmlns="urn:hl7-org:v3"
xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance" xsi:schemaLocation="urn:hl7-org:v3
http://www.fda.gov/oc/datacouncil/schemas/spl/PORR_MT050024.xsd">
```

3.   FPI Sections and Subsections

Information: Sections and subsections have titles and codes.

Terminology: LOINC codes are used for sections and subsections.

SPL location: The title and LOINC codes are associated with the section and subsection.

XML details: The <title> of the sections and subsections and order of the sections and subsections as they appear in the SPL are used to render the FPI Contents. Section <title> is upper case and bold and subsection <title> is title case and bold. The numbering for the sections and subsections are included in the <title> text.

4.   Recent Major Changes in FPI Text

Information: A notation is provided for recent major changes in the FPI text.

Terminology: There is no controlled terminology for this information.

SPL location: The tag is located in the FPI text

XML details: The recent major text is tagged using the <content styleCode="xmChange">. For example:

<text>This is an example of text that is not changed.<content styleCode="xmChange">This is an example of text that is a recent major change</content>This is an example of changed text that is not considered a recent major change</text>

5.   Adverse Drug Reaction Reporting Information

Information: The Highlights includes the company name and contact information (phone number, web site) for reporting suspected drug adverse reactions.

Terminology: There is no controlled terminology for this information.

SPL location: This information is captured in the SPL general header elements.

XML details: The name of the company is represented in the <legalAuthenticator> child of the <document> element. Specific information regarding the company is included through the immediate child elements (descendents) of <legalAuthenticator> as <assignedEntity> and <representedOrganization>. This is illustrated schematically below:
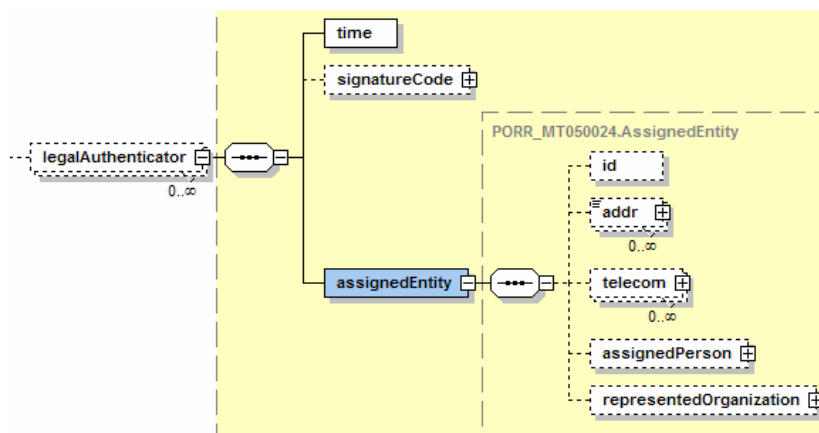
The direct <telecom> children of the <assignedEntity> element are the contact phone numbers and URL for reporting adverse reactions. Note that more than one <telecom> element is permitted as a child of <assignedEntity> , e.g., a phone number and web site URL as separate <telecom> entities.

The following is representative coding for <legalAuthenticator>:

```
<document>
    …..
    …..
    <legalAuthenticator>
        <time/>
        <assignedEntity>
            <telecom value="place the adverse reaction contact phone number here"/>
            <telecom value="place the adverse reaction contact url address here"/>
            <representedOrganization>
                <name>company name here</name>
            </representedOrganization>
        </assignedEntity>
    </legalAuthenticator>
</document>
```

Definitions of elements:

1. <telecom> child of <assignedEntity>: the <telecom> element may be used more than once, however, the first instance should provide the phone number to be used for reporting adverse reactions.
2. <name> child of <representedOrganization>: This should contain the name of the organization as it appears in the Highlights.


6.   Year of Initial US Approval

Information: The Highlights provide the 4 digit year (not day or month) of the initial US approval.

Terminology: There is no controlled terminology for this information.

SPL location: This information is captured in the SPL general header elements.

3

XML details: The 4 digit year of initial US approval as it should appear in Highlights is contained in the <time> child of the <verifier> element. This is illustrated schematically below:
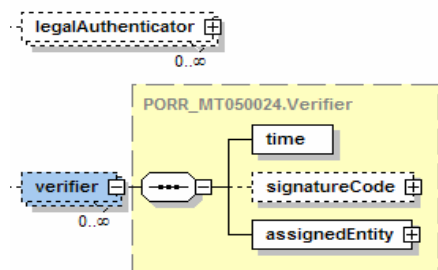
For example:

```
<verifier>
   <time value="2005"/>
   <assignedEntity/>
</verifier>
```

7.   Highlights Text

Information: The actual Highlights of a rendered SPL is constructed from three sources: boilerplate text rendered directly from the stylesheet (e.g., "HIGHLIGHTS OF PRESCRIBING INFORMATION"), data elements inserted into the boilerplate text (e.g., Initial U.S. Approval <year>), and text blocks corresponding to each major highlights part (Highlights text). The Highlights text is captured for Boxed Warning, Recent Major Changes, Indications and Usage, Dosage and Administration, Dosage Forms and Strengths, Contraindications, Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations and Patient Counseling Information.

Terminology: There is no controlled terminology for this information.

SPL location: The text blocks for Highlights are coded with the <excerpt> <highlight> elements of the major section of labeling in which they are contained. For example, the Highlights for Indications and Usage are located with the Indications and Usage section of the labeling. The Highlights text is placed under the main section and not under subsections.

XML details: The text blocks of Highlight are coded with the <excerpt> <highlight> elements of the section in which they are contained. The following is sample coding:

```
<component>
   <section>
      <id root="xxxx"/>
      <code code="43685-7" codeSystem="2.16.840.1.113883.6.1" displayName="Warnings and
      Precautions Section"/>
      <title>5 WARNINGS AND PRECAUTIONS </title>
         <excerpt>
            <highlight>
```

```
<text>
    <list listType="unordered">
        <item>
            Aplastic anemia has been observed in 8% of recipients and is irreversible in the
            majority of patients who experience this. (<linkHtml
            href="#Section_5.1">5.1</linkHtml>)
        </item>
        <item>
            Monitor for hematological adverse reactions every 2 weeks through the second
            month of treatment (<linkHtml href="#Section_5.2">5.2</linkHtml>)
        </item>
    </list>
</text>
</highlight>
</excerpt>
<component>
    <section ID="Section_5.1">
        <id root="xxxx"/>
        <title>5.1 Aplastic anemia</title>
        <text>
            <paragraph>
                Aplastic anemia has been observed in…..
            </paragraph>
        </text>
    </section>
</component>
</section>
</component>
```

The following principles are illustrated by this example:

a. The <text> block for the Highlights is included as the <except> <highlight> <text> children of the respective section. In the example above, the text block rendered in the highlights section is the child of the "Warnings and Precautions" section.
b. The coding of the highlights text block is not in a subsection.
c. The text block is rendered similar to any other text block, although in a location separate from its actual position in the rendered SPL document.
d. Links to the section or subsection where the primary content exists are explicitly entered in the Highlights text block.
e. Section numbering is included in the title of sections and subsections (e.g., '5' and '5.1', above).

8.   Indications

Information: For each indication, the code for the intent of use, indication category and indication are provided.

Terminology: The HL7 terminology is used for Intent of Use. The LOINC code for Medical Problem is used for the indication category. Medical conditions are from the VA/KP Problem List subset.

SPL location: The data elements are under the Indications and Usage section of labeling. If there is more than one indication, the data elements for each indication are under each respective subsection in the Indications and Usage section for the indication.

XML details: The indication being treated is the <subject> of the <excerpt> <highlight> for the indication section or subsection. A <substanceAdminsitration> is the child of <subject>. Coding must contain the intent of use of treatment (<reason>) and the coding of the specific indication being treated (<indicationObservationCriterion>).

The <reason> for treatment is coded via the typeCode attribute of the reason element, e.g., <reason typeCode="TREAT">. The specific indication being treated is coded as the <code> and <value> of the <indicationObservationCriterion>. This is illustrated in the schema diagrams below:
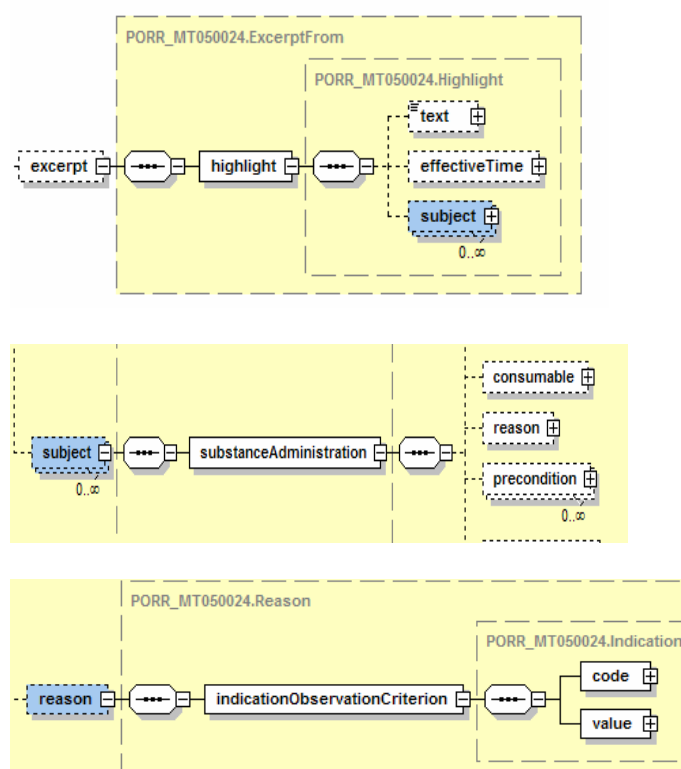
The following is sample coding for this section:

```
<section>
    <excerpt>
        <highlight>
            <subject>
                <substanceAdministration>
                    <reason typeCode="xxxx">
                        <indicationObservationCriterion>
                            <code code="44100-6" codeSystem="2.16.840.1.113883.6.1" displayName="Medical
                            Problem"/>
                            <value xsi:type="CE" code="xxxx" codeSystem="xxxx" displayName="xxxx"/>
                        </indicationObservationCriterion>
```

```
            </reason>
        </substanceAdministration>
      </subject>
    </highlight>
  </excerpt>
</section>
```

Definitions of necessary elements:

1. <reason>: The <reason> element contains the typeCode attribute, which is the intent of use (or desired outcome) of the indication.

2. <indicationObservationCriterion>: The <indicationObservationCriterion> element contains the <code> and <value> children that specify that the indication is for a medical problem and the specific indication being treated. The <code> element contains the code and codeSystem attributes; for the current implementation of SPL, the codeSystem is always coded as follows: <code code="44100-6" codeSystem="2.16.840.1.113883.6.1" displayName="Medical Problem"/>.

The <value> child of <indicationObservationCriterion> contains the code attribute for the actual indication and is coded as <value code="xxxx" codeSystem="xxx" displayName="xxxx"/>.

9.   Maximum Dose

Information: The maximum dose is related to a specific amount of drug over a specific duration of time.

Terminology: UCUM is used for the units of both drug amount and duration of time.

SPL location: The data elements are under the Indications and Usage section of labeling. If there is more than one indication, the data elements for each indication are under the subsection in the Indications and Usage section for the indication.

XML details: Maximum dose is specified as the <maxDoseQuantity> element, a child of <substanceAdministration>:

```
<highlight>
  <subject>
    <substanceAdministration>
    <maxDoseQuantity>
      <numerator value="xxx" unit="xxx"/>
      <denominator value="xxx" unit="xxx"/>
    </maxDoseQuantity>
    <reason…..>
    <precondition…>
    </substanceAdministration>
  </subject>
</highlight>
```

Definitions of necessary elements:

1. <maxDoseQuantity> is coded as 'dose per unit time' of the <numerator> and <denominator> children. For example, "1000 mg per 24 hours" would be coded as:

```
<maxDoseQuantity>
    <numerator value="1000" unit="mg"/>
    <denominator value="24" unit="h"/>
</maxDoseQuantity>
```

10. Condition of Use

Information: There are three types of Condition of Use. One relates to a use of the drug in a selected subgroup of the larger population related to a characteristic of the patient such as the patient's age, race, sex or medical condition. The second relates to the use of the drug only in conjunction with another drug as an adjunct treatment. The third relates to the necessity of specific tests for the selection or monitoring of patients who need the drug.

Terminology: The Precondition Categories are LOINC codes. Sex and race codes are from the NCI Thesaurus. Age is represented by the low and high value. Age range has both a low and high value. The low value alone represents "Age greater than or equal to". The high value alone is used for "Age less than or equal to". Medical conditions are from the VA/KP Problem List subset. Treatments are from FDA SRS, FDA DRLS, and VA NDF-RT. Screening and monitoring tests are from LOINC.

SPL location: The Conditions of Use are coded under sections or subsections where they are described. For example, the data elements may be under the Indications and Usage section of labeling. If there is more than one indication, the data elements for each indication are under the subsection in the Indications and Usage section for that specific indication.

XML details: Conditions of Use are represented by the <precondition> children of <substanceAdministration>. The <precondition> are siblings of <reason>.

```
<subject>
  <substanceAdministration>
      <reason typeCode="xxxx">
         <indicationObservationCriterion>
         ….
         ….
         </indicationObservationCriterion>
      </reason>
      <precondition>
         …
      </precondition>
  </substanceAdministration>
</subject>
```
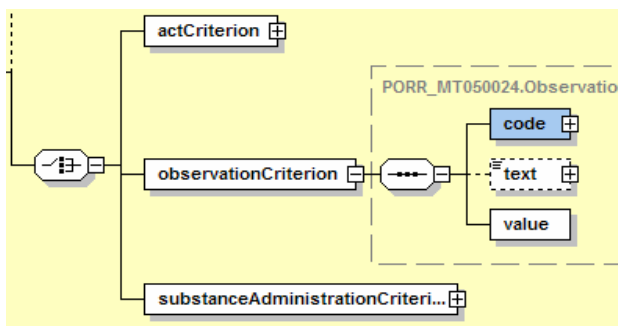
For the purpose of Highlights, children of <precondition> include: <observationCriterion>, and <substanceAdministrationCriterion>. This is illustrated schematically below:
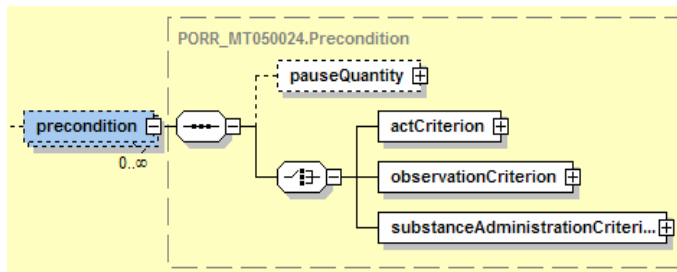
Definitions of necessary elements:

1. <observationCriterion>:

<observationCriterion> is used to code Conditions of Use based on a characteristic of the patient or a test. For a patient characteristic, the <code> is the Precondition category and the <observationCriterion><value> is the specific characteristic of the patient. For a test, the <code> is the LOINC code for the test. The <value> is for the acceptable test result but at this time the value is left blank. This is illustrated schematically below:

For example, an indication for a patient age 6 to 12 is coded as follows:

```
<precondition>
    <observationCriterion>
        <code code="30525-0" codeSystem="2.16.840.1.113883.6.1" displayName="AGE"/>
            <value xsi:type="IVL_PQ">
                <low value="6" unit="a"/>
                <high value="12" unit="a"/>
            </value>
    </observationCriterion>
</precondition>
```
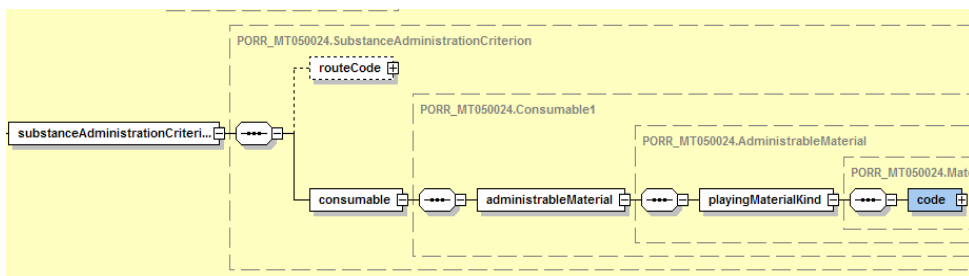
2. <substanceAdministrationCriterion>

The <substanceAdministrationCriterion> is used for the co-administration of another agent as a precondition of use for a specified indication. This element identifies that the coded indication is for use of the product as an adjunct.

An example of coding a <substanceAdministrationCriterion> is illustrated below:

```
<precondition>
   <substanceAdministrationCriterion>
      <consumable>
         <administrableMaterial>
            <playingMaterialKind>
               <code code="xxx" codeSystem="xxx" displayName="xxx"/>
            <playingMaterialKind>
         </administrableMaterial>
      </consumable>
   </substanceAdministrationCriterion>
</precondition>
```

The <code> child of <playingMaterialKind> i.e., <code code="xxx" codeSystem="xxx" displayName="xxx"/>, can be an ingredient using the FDA SRS code system, a drug product using the FDA DRLS code system, or a pharmacological class using the VA NDF-RT code system.
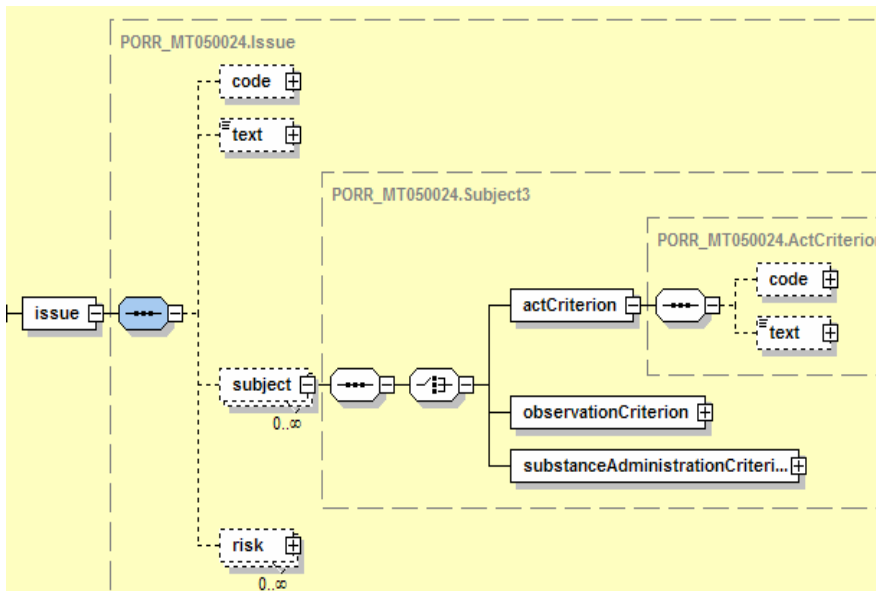
11.   Limitation of Use

Information: There are a number of categories for Limitation of Use such as contraindications and these may relate to a characteristic of the patient such as the patient's age, race, sex or medical condition.

Terminology: The Limitation of Use categories are from the NCI Thesaurus. Precondition Categories are LOINC codes. Sex and race codes are from the NCI Thesaurus. Medical conditions are from the VA/KP Problem List subset. Age is represented as a range with a low and high value. The low value alone represents "Age greater than or equal to". The high value alone is used for "Age less than or equal to".

SPL location: The Limitations of Use are coded under the sections or subsections where they are described. For example, the data elements may be under the Indications and Usage section of labeling if this is where the Limitation of Use is described.

XML details: Limitations of Use are coded as <issue> within the indication highlight excerpt. The general structure is shown schematically as follows:

The following is an example of generic coding of an issue:

```
<section>
   <excerpt>
      <highlight>
         <subject>
            <substanceAdministration>
               <subjectOf>      <!-- Limitation of Use ->
                  <issue>
                     <code code="xxx" codeSystem="xxx" displayName="xxxx"/>
                     <subject>    <!—Example with an Observation Criterion ->
                        <observationCriterion>
                           <code code="xxx" codeSystem="xxx" displayName="xxxx"/>
                           <value xsi:type="CE"  code="xxxx" codeSystem="xxx" displayName="xxxx"/>
                        </observationCriterion>
                     </subject>
                  </issue>
               </subjectOf>
            </substanceAdministration>
         </subject>
      </highlight>
   </excerpt>
</section>
```

Each <issue> 'category is identified by the code attribute of the <code> child element of <issue> as in the following example:

```
<issue>
<code code="C50646" codeSystem="2.16.840.1.113883.3.26.1.1"
displayName="CONTRAINDICATION"/>
```

The <subject> within an <issue> for a Limitation of Use is coded identically to that for a <precondition> for a Condition of Use.

12.   Drug Interaction

Information: Interactions have a contributing factor such as food or another drug and a consequence such as a medical condition.

Terminology: The Limitation of Use/Issue category code for interaction is used. Contributing factors are from FDA SRS (food or drug ingredients), FDA DRLS (specific drug products), VA NDF-RT (pharmacological class), and NCI Thesaurus (general substance such as "food"). Types of consequences are from the NCI Thesaurus. Pharmacokinetic effects are from the NCI Thesaurus. Medical conditions are from the VA/KP Problem List subset.

SPL location: The data elements are coded under the section or subsection where the interaction is described. The same data elements may be represented in more than one place in the labeling.

XML details: Interactions include contributing factors and consequences.

12.1.   Contributing factors

Interactions are coded as <issue>s. Similar to coding of <issue>s within indications, these are coded within the <excerpt> <highlight> of a section or subsection. The schematic representation of an issue is reproduced below:
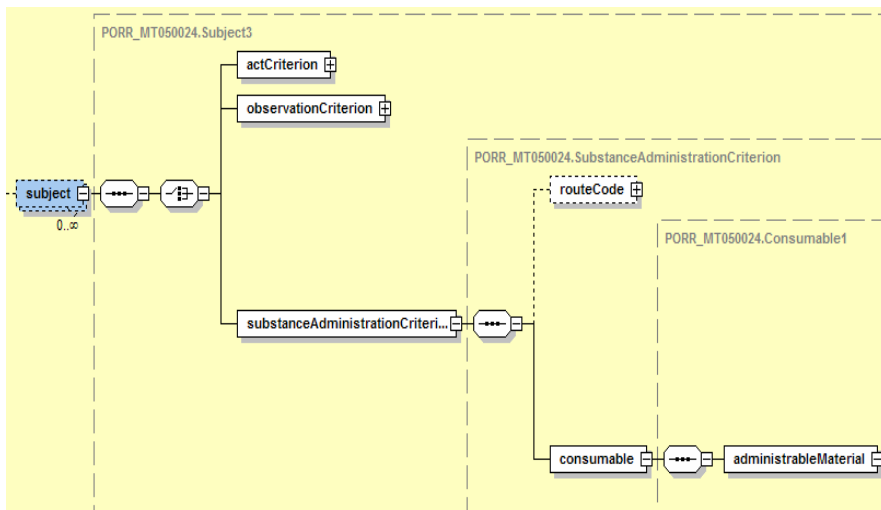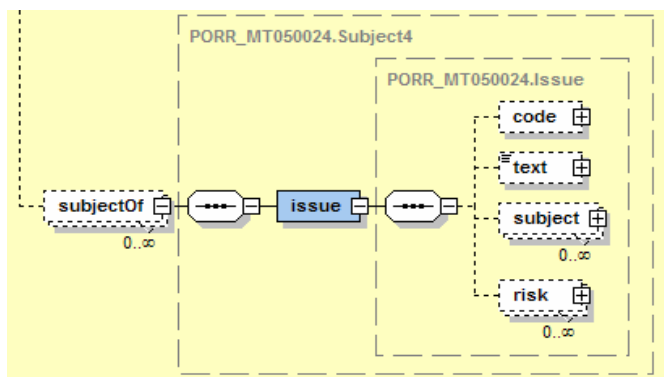
For SPL, the subject of interactions is a <substanceAdministration>.

```
<excerpt>
   <highlight>
      <subject>
         <substanceAdministration>
            <subjectOf>
               <issue>
                  <code code="xxx" codeSystem="xxx" displayName="xxx"/>
                     <subject>
                        <substanceAdministrationCriterion>
                           <consumable>
                              <administrableMaterial>
                                 <playingMaterialKind>
                                    <code code="xxx" codeSystem="xxx" displayName="xxx"/>
                                 </playingMaterialKind>
                              </administrableMaterial>
                           </consumable>
                        </substanceAdministrationCriterion>
                     </subject>
                     <risk>
                      ….. <!—described below>
                     </risk>
               </issue>
            </subjectOf>
         </substanceAdministration>
      </subject>
   </highlight>
</excerpt>
```

Definitions of necessary elements:

1. The <code element child of issue contains the Limitation of Use category code for interaction.

2. The <code> element for <playingMaterialKind> reflects the 'contributing factor' for an interaction.

3. Multiple <subject>s (contributing factors) can be associated with a single <issue>; therefore, if several contributing factors are identified as associated with a single <risk>, these can be coded as multiple <subject>s for one or many <risk>. Similarly, a single <subject> can be coded with multiple <risk>s, or multiple <subject>s can be coded with multiple <risk>s. For example, in the setting where a set of interactions all have a similar set of consequences of the interaction.

12.2. Consequences

Consequences of an interaction are coded as <risk>s, a sibling to the <subject> of an <issue>. This includes different types of consequences such as patient problems or pharmacokinetic effects. These are coded as <risk> <consequenceObservation> s:

```
<issue>
   <subject>
   …..
   </subject>
   <risk>
      <consequenceObservation>
         <code code= "xxxx" codeSystem="xxxx" displayName="xxxx"/>
         <value xsi:type="CE"  code= "xxxx" codeSystem="xxx" displayName="xxxx"/>
      </consequenceObservation>
   </risk>
</issue>
```

Definitions of necessary elements:

1. <code> <value>. The <code> <value> pair identifies the actual outcome of the interaction where the <code> is the type of consequence and the <value> is the consequence.

2. Multiple <subject>s (contributing factors) can be associated with a single <issue>; therefore, if several contributing factors are identified as associated with a single <risk>, these can be coded as multiple <subject>s for one or many <risk>. Similarly, a single <subject> can be coded with multiple <risk>s, or multiple <subject>s can be coded with multiple <risk>s. For example, in the setting where a set of interactions all have a similar set of consequences of the interaction.

13. Adverse Reaction

Information: Adverse Reactions have a medical condition consequence.

Terminology: The Limitation of Use/Issue category code for adverse reaction is used. The only type of consequence is a "Patient problem" from the NCI Thesaurus. Medical conditions are from the VA/KP Problem List subset.

SPL location: The data elements are coded under the section or subsection where the adverse reaction is described. The same data elements may be represented in more than one place in the labeling.

XML details: Adverse reactions are coded as described as the consequence of an interaction. The <code> or type of consequence is a Patient Problem. The <value> is the consequence.

14. Pharmacological Class

Information: Active ingredients and products may be described by pharmacological class.

Terminology: The VA NDF-RT is used for the pharmacological class.

SPL location: The pharmacological class for an ingredient is coded under the drug listing data element for the active ingredient. The pharmacological class for a product is coded under the Drug Listing data element for the manufactured medicine.

XML details: Pharmacological class is coded under active ingredient or product.

14.1. Active ingredient

The pharmacological class of an active ingredient is the coded as <generalizedPharmaceuticalClass> a child of <activeIngredientSubstance><asSpecializedKind> as described below:

```
<manufacturedMedicine>
   <activeIngredient>
      <activeIngredientSubstance>
         <asSpecializedKind>
            <generalizedPharmaceuticalClass>
               <code code="xxxx" codeSystem="xxx" displayName="xxx"/>
            </generalizedPharmaceuticalClass>
         </asSpecializedKind>
      </activeIngredientSubstance>
   </activeIngredient>
</manufacturedMedicine>
```

Definition of elements

1. An ingredient may have zero to many pharmacological classes. Each one is described with a new <asSpecializedKind> element.

14.2. Product

The pharmacological class of the overall <manufacturedMedicine> is coded as <generalizedPharmaceuticalClass> , a child of <activeIngredientSubstance><specializedKind> as described below:

```
<manufacturedMedicine>
   <asSpecializedKind>
      <generalizedPharmaceuticalClass>
         <code code="xxxx" codeSystem="xxx" displayName="xxx"/>
      </generalizedPharmaceuticalClass>
   </asSpecializedKind>
</manufacturedMedicine>
```

Definition of elements

1. A product may have zero to many pharmacological classes. Each one is described with a new <asSpecializedKind> element.